

The Evolution of Covered Stents

Improving the outcomes of PTA for hemodialysis access circuit stenosis with the FLAIR® Endovascular Stent Graft, FLUENCY® PLUS Stent Graft, and COVERA™ Vascular Covered Stent.

BY BART DOLMATCH, MD, FSIR

Arteriovenous (AV) access is the lifeline for patients with end-stage renal disease who require chronic hemodialysis. Today, there are nearly 500,000 people with end-stage renal disease in the United States and many thousands more throughout the world who undergo hemodialysis, most of whom dialyze with either an AV graft (AVG) or AV fistula (AVF).^{1,2} However, these permanent dialysis access circuits are fraught with problems, particularly the development of flow-limiting stenosis. Dialysis access stenosis reduces dialysis efficiency and can cause secondary dialysis circuit complications, such as bleeding, aneurysms, and pseudoaneurysms. In some cases, stenosis can lead to access circuit thrombosis, necessitating urgent declotting or abandonment with central venous catheter placement when declotting cannot be achieved.

BACKGROUND

Percutaneous transluminal angioplasty (PTA) has been the mainstay for treating stenosis in AVGs and AVFs. Dialysis access PTA, first described by Glanz et al in 1984,³ is still widely used to treat stenosis. It is usually performed as an outpatient procedure and is easily arranged, safe, and technically effective in treating stenosis so that the patient can return to dialysis with good AVG or AVF function. However, recurrence of stenosis at the PTA site is frequent, necessitating repeated PTA.

In the early 1990s, there was hope that adding a bare-metal stent (BMS) at the time of PTA would confer better post-PTA patency. There have been only three truly randomized studies comparing PTA with PTA plus a BMS, and the results indicated no clear patency advantage when a BMS was added.⁴⁻⁶ Therefore, a BMS does not improve patency if PTA has been technically successful and is only recommended for bailout of technically failed PTA.⁷

Covered stents were initially developed to treat abdominal aortic aneurysms (AAAs).⁸ Also called stent grafts or endografts, these AAA devices require large-caliber delivery systems, have pins or hooks at the ends of the device to achieve secure fixation, and incorporate graft material to prevent leakage of blood into the aneurysm sac. Concurrent with initial experience using AAA endografts, reports were

published describing the use of smaller-diameter covered stents in peripheral blood vessels to treat aneurysms and traumatic AVFs. An early article by Marin et al described successful treatment of a traumatic femoral AVF using a homemade covered stent.⁹ Subsequent reports described the use of various types of covered stents to treat a variety of peripheral vascular conditions, including traumatic injuries, pseudoaneurysms, aneurysms, and peripheral artery occlusive disease.¹⁰

The concept that a stent covered with graft material could prevent or limit the development of restenotic tissue evolved over the ensuing years. There were several areas where post-PTA restenosis was frequently encountered, including coronary artery and peripheral artery interventions, transjugular intrahepatic portosystemic shunts, and dialysis access circuit interventions. Covered stents have limited use in the coronary arteries and are prone to thrombosis.¹¹ In the peripheral arteries, aortoiliac and femoropopliteal covered stents have been adopted. However, in both the coronary and peripheral arteries, inhibition of restenosis is now often managed with pharmacologic approaches such as drug-eluting stents and drug-coated balloons. Yet, covered stents remain the mainstay for preventing restenosis in transjugular intrahepatic portosystemic shunts and dialysis access circuits.

A BROADER STENT GRAFT APPLICATION

Focusing on hemodialysis access circuit stenosis, early work on AVG and AVF covered stents began in the mid-1990s with in vivo studies of covered stent designs and healing properties.¹²⁻¹⁵ Various graft materials were studied, as were constructs where the graft material was on the outside, inside, or both sides of a stent. Different stents were also modeled in the covered stent design. From this work, an understanding of covered stent design and healing in peripheral arteries created the foundation that led to development of the hemodialysis access circuit covered stents we use today.

The FLAIR® and FLUENCY® PLUS Endovascular Stent Grafts

In the late 1990s, covered stents seemed to be a viable approach to limit post-PTA restenosis in AV access circuits.

Sponsored by BD

Based on healing properties with different materials and designs, prototype devices were developed and tested by the collaborative efforts at Impra, Inc. and AngioMed GmbH & Co., which were both acquired by C.R. Bard, Inc., now Becton, Dickinson and Company. This work resulted in the first commercially available AV access covered stent in United States, called the FLAIR® Endovascular Stent Graft (BD). Designed on a self-expanding nitinol stent embedded in a fused internal-external barrier layer of expanded polytetrafluoroethylene (ePTFE), the FLAIR® Stent Graft was specifically developed to treat stenosis at the venous end of an AVG, where recurrent post-PTA restenosis was often seen. One novel attribute of the FLAIR® Stent Graft was the option to select either a tubular or flared configuration depending on the size of the outflow vein. The flared device has a downstream diameter that is 4 mm larger than the rest of the device. This larger flared end of the stent graft was a better match for the size of the outflow veins, which permitted optimized flow patterns that could lead to decreased neointimal hyperplasia formation.

An additional advantage that wasn't recognized during the design of the flared FLAIR® Stent Graft is its ability to support more laminar flow with fewer flow disturbances within the venous outflow, as compared with the straight configuration in the same condition where the outflow vein has a larger diameter than the AVG. As the diameter of the device increases, so does the cross-sectional area, and therefore the velocity of blood flow entering the vein diminishes. Simulated flow models have shown that the typical tubular end-to-side vein/graft anastomosis produces turbulence at the anastomosis, whereas placement of a flared FLAIR® Stent Graft at the anastomosis allows for more laminar flow into the outflow vein.¹⁶ Turbulent flow has been associated with the development of neointimal stenosis, whereas laminar flow is believed to reduce hyperplastic tissue proliferation and may reduce the development of restenosis.

The FLAIR pivotal trial and the subsequent RENOVA postmarket trial demonstrated clinical benefit using the FLAIR® Stent Graft to treat AVG venous anastomotic stenosis. Both trials showed superior treatment site patency and AVG circuit patency compared with PTA alone at 6 months.^{17,18} The FLAIR® Stent Graft was approved by the FDA in 2007 for use in the treatment of stenoses at the venous anastomosis of ePTFE or other synthetic AVGs.

The FLUENCY® PLUS Endovascular Stent Graft (BD) was developed at the same time as the FLAIR® Stent Graft on a slightly different self-expanding base stent. The FLUENCY® PLUS Stent Graft was tested for treatment of in-stent restenosis located in the venous outflow of AVGs and AVFs, as well as in-stent restenosis in the central veins. Compared with PTA at 6 months, the FLUENCY® PLUS Stent Graft demonstrated superior patency in both the AV access circuit and central

veins.¹⁹ Beyond treatment of in-stent restenosis, the FLUENCY® PLUS Stent Graft was approved by the FDA for use in the venous outflow of AVGs without any previous stent placement. The FLUENCY® PLUS Stent Graft still remains the only proven treatment studied in a clinical trial for treating in-stent restenosis in hemodialysis access circuits and central veins.²⁰

Although these stent grafts are superior to PTA for their indicated applications, both the FLAIR® Stent Graft and FLUENCY® PLUS Stent Graft have been in clinical use for more than 10 years without much change. Meanwhile, today's requirements for dialysis circuit intervention have evolved. Whereas the FLAIR® Stent Graft was developed for AVG use, the impact of the Fistula First Breakthrough Initiative has led to fewer AVGs and many more AVFs. Furthermore, with recognition that BMSs do not afford better outcomes than PTA, fewer BMSs are seen in AV circuits, and there is a decreased need for the FLUENCY® PLUS Stent Graft to treat in-stent restenosis. What is needed at this time is a flexible covered stent with a broad sizing matrix that can be accurately delivered to treat not only stenosis in AVGs but also in AVFs.

The COVERA™ Vascular Covered Stent

To meet this need, BD/Bard developed the COVERA™ Vascular Covered Stent, which has a flexible, nitinol base stent that has excellent conformability and is kink resistant and durable. Although it uses a similar ePTFE covering as the FLAIR® Stent Graft and FLUENCY® PLUS Stent Graft, the COVERA™ Vascular Covered Stent is an improvement in several ways. The size matrix of the COVERA™ Vascular Covered Stent is broad and allows treatment of long lesions. The delivery system is triaxial and permits precise implantation, yet it has a smaller diameter than comparable delivery catheters for the FLAIR® Stent Graft and FLUENCY® PLUS Stent Graft.

The COVERA™ Vascular Covered Stent has been approved by the FDA for use in AVGs and AVFs based on data from the ongoing AVEVA and AVEVEW clinical trials. The AVEVA trial is a single-arm nonrandomized clinical study that evaluated the COVERA™ Vascular Covered Stent for treatment of AVG venous outflow stenosis.²¹ The 6-month results exceeded the predicted patency goal of 40% at 6 months with a treatment site patency of 71%, which was better than results from both the FLAIR pivotal and RENOVA clinical trials. AVEVA has completed its 12-month data review and will soon complete 24-month follow-up data.

The AVEVEW clinical trial is a prospective, randomized, multicenter study comparing the outcome of intervention in AVFs.²² Randomized between PTA or PTA with the COVERA™ Vascular Covered Stent, 280 patients were enrolled in the trial and, at 6 months, demonstrated a target lesion primary patency rate of 78.7% for the COVERA™ Vascular

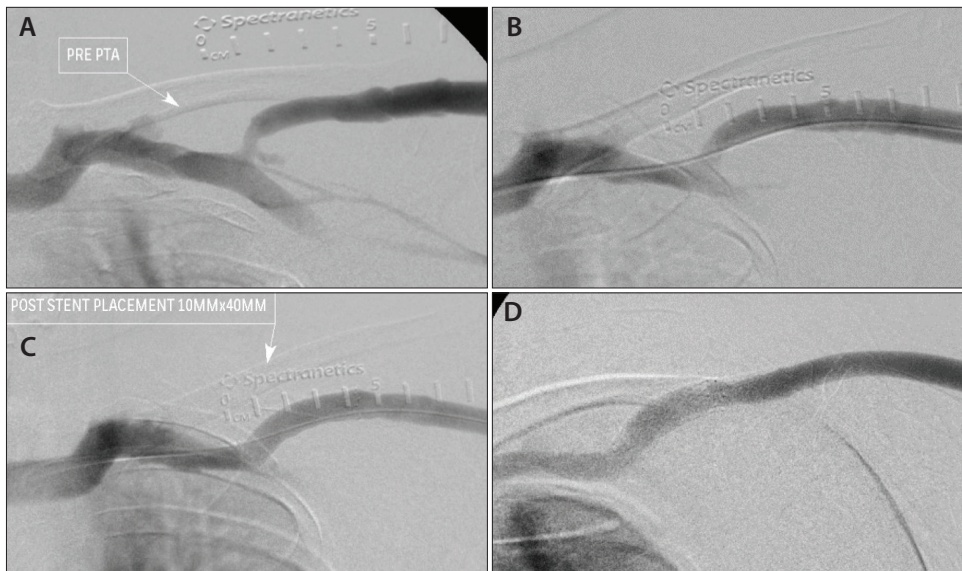


Figure 1. Stenosis > 50% at the terminus of the left cephalic vein arch prior to PTA (A). Post-PTA result with acceptable improvement, although there is some residual stenosis (B). A 10- X 40-mm COVERA™ Vascular Covered Stent was placed at the site of PTA, with no residual stenosis. The COVERA™ Vascular Covered Stent was placed with precision, treating the entire arch, but not extending into the axillary or subclavian vein (C). A look at the COVERA™ Vascular Covered Stent 5 months postprocedure during intervention elsewhere in the AVF. The COVERA™ Vascular Covered Stent remains widely patent (D).

Covered Stent compared with 47.9% for standard PTA. The 12-month results show superior patency for the COVERA™ group at all treatment sites, with over 35% greater patency at 12 months (57.5% for COVERA™ Vascular Covered Stent vs 21.2% for standard PTA). At 6 months, half of all stenoses were in the cephalic vein arch, but all stenosis locations had statistically superior patency with the COVERA™ Vascular Covered Stent compared with PTA alone for all subgroups analyzed. Figure 1 shows one of the cephalic arch stenosis cases from the AVeNEW trial. Data collection and analysis will continue to 24 months.

CONCLUSION

Covered stents have consistently improved the results of PTA for treating hemodialysis access circuit stenosis. For more than 10 years, BD/Bard has advanced the science of covered stents. Three different covered stents have been developed, tested, and proven in human clinical trials: the FLAIR® Stent Graft, FLUENCY® PLUS Stent Graft, and now the COVERA™ Vascular Covered Stent. With recent compelling clinical trial data and FDA approval, the COVERA™ Vascular Covered Stent can be used to treat stenosis in both AVGs and AVFs. ■

1. United States Renal Data System (USRDS). 2018 USRDS annual data report: epidemiology of kidney disease in the United States. Chapter 1: incidence, prevalence, patient characteristics, and treatment modalities. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018. https://www.usrds.org/2018/view/v2_01.aspx. Accessed July 23, 2019.
2. United States Renal Data System (USRDS). 2018 USRDS annual data report: epidemiology of kidney disease in the United States. Chapter 3: vascular access. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018. https://www.usrds.org/2018/view/v2_03.aspx. Accessed July 23, 2019.
3. Glanz S, Gordon D, Butt KM, et al. Dialysis access fistulas: treatment of stenoses by transluminal angioplasty. *Radiology*. 1984;152:637-642.
4. Quinn SF, Schuman ES, Demlow TA, et al. Percutaneous transluminal angioplasty versus endovascular stent placement in the treatment of venous stenoses in patients undergoing hemodialysis: intermediate results. *J Vasc Interv Radiol*. 1995;6:851-855.
5. Beathard GA. Gianturco self-expanding stent in the treatment of stenosis in dialysis access grafts. *Kidney Int*. 1993;43:872-877.

6. Hoffer EK, Sultan S, Herskowitz MM, et al. Prospective randomized trial of a metallic intravascular stent in hemodialysis graft maintenance. *J Vasc Interv Radiol*. 1997;8:965-973.
7. National Kidney Foundation. 2006 updates: clinical practice guidelines and recommendations. http://www.kidney.org/sites/default/files/docs/12-50-0210_jag_dcp_guidelines-hd_oct06_sectiona_ofc.pdf. Accessed July 11, 2019.
8. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg*. 1991;5:491-499.
9. Marin ML, Veith FJ, Panetta TF, et al. Percutaneous transfemoral insertion of a stented graft to repair a traumatic femoral arteriovenous fistula. *J Vasc Surg*. 1993;18:299-302.
10. Marin ML, Veith FJ, Cynamon J, et al. Initial experience with transluminally placed endovascular grafts for the treatment of complex vascular lesions. *Ann Surg*. 1995;222:449-469; discussion 465-469.
11. Lee WC, Hsueh SK, Fang CY, et al. Clinical outcomes following covered stent for the treatment of coronary artery perforation. *J Interv Cardiol*. 2016;29:569-575.
12. Dolmatch BL, Tio FO, Li XD, Dong YH. Patency and tissue response related to two types of polytetrafluoroethylene-covered stents in the dog. *J Vasc Interv Radiol*. 1996;7:641-649.
13. Dolmatch BL, Dong YH, Trierotola SO, et al. Tissue response to covered WallStents. *J Vasc Interv Radiol*. 1998;9:471-478.
14. Virmani R, Kolodgie FD, Dake MD, et al. Histopathologic evaluation of an expanded polytetrafluoroethylene-nitinol stent endoprosthesis in canine iliofemoral arteries. *J Vasc Interv Radiol*. 1999;10:445-456.
15. Dolmatch B, Dong YH, Heeter Z. Evaluation of three polytetrafluoroethylene stent-grafts in a model of neointimal hyperplasia. *J Vasc Interv Radiol*. 2007;18:527-534.
16. Scholz H, Krueger U. Report on comparison of straight versus flared stent grafts by computational fluid dynamic. Queen Elisabeth Hospital, Berlin, Germany. Data on file, BD Interventional.
17. Haskal ZJ, Trierotola S, Dolmatch B, et al. Stent graft versus balloon angioplasty for failing dialysis-access grafts. *N Engl J Med*. 2010;362:494-503.
18. Haskal ZJ, Saad TF, Hoggard JG, et al. Prospective, randomized, concurrently-controlled study of a stent graft versus balloon angioplasty for treatment of arteriovenous access graft stenosis: 2-year results of the RENOVA study. *J Vasc Interv Radiol*. 2016;27:1105-1114.e3.
19. Falk A, Maya ID, Yevzlin AS, and RESCUE Investigators. A prospective, randomized study of an expanded polytetrafluoroethylene stent graft versus balloon angioplasty for in-stent restenosis in arteriovenous grafts and fistulae: two-year results of the RESCUE study. *J Vasc Interv Radiol*. 2016;27:1465-1476.
20. US Food & Drug Administration. Premarket approval – PMA. <https://www.accessdata.fda.gov/scripts/cdrh/cdohs/cfpma/TextResults.cfm?c=aW4tc3RlbnQgcmlVzdGVub3Npcw==&sc=8&pn=25>. Accessed July 12, 2019.
21. Clinical study of the BARD® COVERA™ arteriovenous (AV) stent graft in AV graft patients (AVeVA) (AVeVA). <https://clinicaltrials.gov/ct2/show/NCT02790606>. Accessed July 12, 2019.
22. Clinical study of the BARD® COVERA™ arteriovenous (AV) stent graft (AVeNEW). <https://clinicaltrials.gov/ct2/show/NCT02649946>. Accessed July 12, 2019.

Bart Dolmatch, MD, FSIR
Interventional Radiologist
Palo Alto Medical Foundation
Mountain View, California
duster54@sbcglobal.net

Disclosures: Consultant to and speaker and investigator for BD.